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Original Article

Efficacy of PET/CT to exclude leiomyoma in patients with lesions suspicious for uterine sarcoma on MRI

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ABSTRACT

Objective: To analyze the efficacy of positron emission tomography/computed tomography (PET/CT) for the diagnosis of uterine sarcoma.

Materials and methods: Thirty-four patients evaluated between January 2010 and March 2015 were retrospectively enrolled. All patients in whom uterine sarcoma was suspected based on contrast-enhanced magnetic resonance imaging (MRI) findings (heterogeneous, high signal intensity on T2-weighted images and/or high intensity on T1-weighted images) underwent PET/CT for further assessment. Patients were divided into 2 groups based on postoperative pathological findings: uterine sarcoma (n = 15) and leiomyoma (n = 19). The maximum standardized uptake value (SUVmax) of all lesions was measured using PET/CT; we calculated the optimal cutoff value for diagnosing sarcoma.

Results: The median SUVmax for uterine sarcoma and leiomyoma was 12 and 4.1, respectively; these values were significantly different. An SUVmax of greater than 7.5 was able to exclude leiomyoma with 80.8% sensitivity and 100% specificity (area under the curve, 95.3%). A cutoff SUVmax of 7.5 yields 100% specificity, and a cutoff SUVmax of 4.4 yields a 100% negative predictive value (NPV). The combination of PET/CT and lactate dehydrogenase (LDH) levels had a sensitivity of 86.6%, specificity of 100%, positive predictive value of 100%, and an NPV of 90.4%. No relation between histopathology or International Federation of Gynecology and Obstetrics (FIGO) stage and 18-fluoro-2-deoxy-D-glucose uptake value on PET/CT was seen. The surgical outcome trended toward a correlation with the SUVmax, although this was not statistically significant.

Conclusions: In patients with MRI findings consistent with either uterine sarcoma or leiomyoma, PET/CT can decrease the false-positive rate by setting an optimal cutoff SUVmax of 7.5. Using this cutoff can avoid unnecessary surgery.

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Introduction

Uterine sarcomas are rare, accounting for 3–7% of uterine cancers [1]. They are classified as either leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), undifferentiated endometrial stromal sarcoma (UES), or adenosarcoma (AS). Uterine sarcomas have a poor prognosis, significantly worse than that of endometrial cancer [1], although ESS and AS have more favorable outcomes than the other subtypes, with a low incidence of recurrence. Some subtypes exhibit abnormal bleeding in the early phase and can be diagnosed using endometrial curettage. However, LMS and UES have similar symptoms to leiomyoma, and these subtypes are not amenable to diagnosis by endometrial sampling [2]. To differentiate lesions with a high risk for uterine sarcoma, primary screening is conducted using symptoms, physical examination findings, tumor size, serum lactate dehydrogenase (LDH) levels, and ultrasound; secondary screening uses magnetic resonance imaging (MRI). It is important to distinguish uterine sarcoma from leiomyoma because of the difference in treatment: leiomyomata have the option for conservative management while sarcomas require surgical treatment. An accurate diagnosis can help patients avoid unnecessary surgery. However, once a uterine tumor is suspected of malignancy,

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surgical intervention with histopathological examination is necessary.

MRI is a well-known diagnostic tool for uterine sarcoma. Sarcomas have a heterogeneous appearance of high signal intensity on T2-weighted images (T2-WI) and/or high signal intensity on T1-weighted images (T1-WI). These findings imply necrosis or hemorrhage of muscle or mesenchymal tissue, but they are not specific to sarcomatous lesions.

Positron emission tomography (PET) is a metabolic imaging modality that uses positron tracers such as 18-fluoro-2-deoxy-D-glucose (^{18}F-FDG). Using FDG PET alone or PET combined with computed tomography (PET/CT) has been increasingly employed for the detection of uterine tumors. Although some authors report the efficacy of PET to detect tumor recurrence in patients with uterine sarcoma, the rarity of the tumors means that little is known about the role of PET in the primary assessment of uterine sarcomas [3,4].

In our institution, patients with lesions suspicious for uterine sarcoma on MRI are sent for confirmation with PET/CT. We retrospectively reviewed the surveillance of uterine tumors using PET/CT and determined the optimal cutoff for the maximum standardized uptake value (SUVmax) to differentiate uterine sarcoma from leiomyoma.

Materials and methods

Patients

Thirty-four patients who were evaluated at Juntendo University Hospital between January 2010 and March 2015 were retrospectively enrolled. Informed consent was obtained from all patients. All patients with lesions suspicious for uterine sarcoma on contrast-enhanced MRI (heterogeneous, high signal intensity on T2-WI and/or high intensity on T1-WI) underwent PET/CT for further assessment. All enrolled patients underwent surgery, and the pathological findings were used to divide them into 2 groups: those with uterine sarcoma and those with leiomyoma. We analyzed the clinical symptoms and signs such as uterine enlargement, abnormal bleeding, tumor size, and serum LDH and cancer antigen (CA) 125 levels in both groups.

PET/CT

All scans were performed using a GE Discovery STE PET/CT (GE Medical Systems, Inc., Milwaukee, WI). Each patient was administered 3.7 MBq/kg ^{18}F-FDG after a 6-h fast and imaged after a 60-min uptake period. Whole-body PET imaging was then performed from the skull base to the upper thighs using 2-dimensional mode, at 3.5 min per each of 6 bed positions, depending on the size of the patient. CT images were acquired over the same range using a pitch of 1.375 mm, 140 kV (peak), 20–300 mA current, and 3.75-mm slices.

MRI

All examinations were performed using a 3 T MRI scanner (MAGNETOM Spectra; Siemens Healthcare GmbH, Erlangen, Germany) equipped with a 16-channel phased array body coil. The pelvic MRI protocol included axial T1-WI sequences (repetition time [TR]/echo time [TE], 550/10 ms; matrix size, 448 × 269; field of view [FOV], 250 mm), T1-WI with fat suppression (TR/TE, 650/13 ms; matrix size, 384 × 230; FOV, 250 mm), diffusion-weighted imaging (DWI) (TR/TE, 6000/77 ms; matrix size, 128 × 80; b values, 0 and 800 s/mm^2; FOV, 400 mm), sagittal T2-WI sequences (TR/TE, 4000/90 ms; matrix size, 448 × 314; FOV, 250 mm), and axial and sagittal contrast-enhanced T1-WI with fat suppression (axial TR/TE, 700/10 ms; matrix size, 384 × 230; FOV, 250 mm; sagittal TR/TE, 680/10 ms; matrix size, 384 × 230; FOV, 250 mm). All images used 5–6 mm section thickness.

SUVmax

The SUVmax of all lesions was measured using PET/CT and compared between groups. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff value for differentiating uterine sarcoma from leiomyoma. Overall survival was analyzed by distribution into low and high SUVmax values, divided by the optimal cutoff value.

Statistical analysis

All statistical analyses were performed using XL STAT software (Addinsoft, Paris, France). Student's t-test was used to compare differences between groups. ROC curve analysis was performed to determine the optimal SUVmax cutoff points for differentiation between uterine sarcoma and leiomyoma. A P value of <0.05 was defined as significant.

Results

Patient characteristics are listed in Tables 1–3. Of the 34 patients with MRI findings suspicious for uterine sarcoma, 15 were diagnosed with sarcoma and 19 were diagnosed with leiomyoma. Of the 15 patients in the sarcoma group, 6 had LMS, 4 had UES, 4 had ESS, and 1 had AS (Figs. 1 and 2); of the 19 patients in the leiomyoma group, 10 had ordinary leiomyomata, 6 had degenerated leiomyomata, and 3 had cellular leiomyomata. The patients in the sarcoma group were significantly older ($P = 0.001$) and had higher LDH levels ($P = 0.001$) and higher FDG uptake values on PET/CT ($P = 0.001$) than those in the leiomyoma group.

Using the ROC curve, a SUVmax greater than 7.5 was able to exclude leiomyoma with 73.3% sensitivity, 100% specificity, 100% positive predictive value (PPV), and 82.6% negative predictive value (NPV) (area under the curve, 93.3%) (Fig. 3).

The sensitivity, specificity, PPV, and NPV of the LDH level were 53.3%, 86.3%, 72.7%, and 73%, respectively; the respective values for CA125 levels were 64.2%, 70.5%, 64.2%, and 70.5%. The combination of PET/CT and LDH had a sensitivity of 86.6%, specificity of 100%, PPV of 100%, and NPV of 90.4%. The histopathology and

Table 1
Characteristics of patients.

	Uterine sarcoma (n = 15)	Leimyoma (n = 19)	*P*-value
Age, mean ± SD, years	55.8 ± 11.4	45 ± 7.0	$P = 0.001$
Tumor size, mean ± SD, cm	12.0 ± 6.5	13.8 ± 4.9	N.S
Metrorrhagia	12	3	N.S
Level of LDH (mean ± SD)	343 ± 188	183.1 ± 44	$P = 0.001$
Lavel of CA125 median (range)	44 (7–206)	26 (7–108)	N.S
SUVmax of PET/CT	15.1 ± 12.6	4.0 ± 2.4	$P = 0.001$
Histopathological			
LMS	6		
ESS	4		
UES	4		
Adenosarcoma	1		
Originary leiomyoma		10	
Degenerated leiomyoma		6	
Cellular leiomyoma		3	

LMS: Leiomyosarcoma, ESS: Endometrial stromal sarcoma, UES: Undifferentiated endometrial sarcoma.

Table 2
Characteristics of uterine sarcoma cases (n = 15).

No.	Age (years)	Pathology	Timor size (cm)	LDH (IU/l)	MRI findings			FDG uptake (SUVmax)	FIGO stage
					T1-WI	T2-WI	DWI		
1	57	LMS	15	653	High	High		14.5	4
2	56	LMS	23	155	High	High		10	3
3	48	LMS	8	541	High	High		10.9	2
4	57	LMS	24	586	High	High		16	3
5	49	LMS	16	519	High	High	High	27	4
6	59	LMS	7	274	Low	High		8.5	4
7	60	ESS HG	8.5	141	High	High	High	9.6	1
8	66	ESS HG	20	368	High	High		4.9	3
9	60	ESS HG	14	495	High	High		26.13	2
10	70	ESS HG	15	512	High	High		19.2	4
11	29	ESS	6.5	124	Low	High		4.6	1
12	54	ESS	4	147	High	High		6.34	1
13	77	ESS	9	232	High	High		53	1
14	42	ESS	5	172	Low	High	High	8.8	1
15	54	Adenosarcoma	6	228	High	High		7.4	1

Table 3
Characteristics of leiomyoma cases (n = 19).

No.	Age (years)	Pathology	Tumor size (cm)	LDH (IU/l)	MRI findings			ADC	FDG uptake (SUVmax)
					T1-WI	T2-WI	DWI		
1	49	C	14	146	High	High			3.4
2	41	C	24	169	Low	High	High		5.99
3	47	C	15	258	High	High			3.9
4	39	D	8	136	High	High			1.2
5	46	D	13	200	Low	High	High		4.4
6	34	D	12	166	Low	High	High		6.08
7	38	D	12	303	Low	High	High	Low	7.5
8	40	D	11	195	High	High			6.8
9	43	D	20	180	High	High			4.1
10	61	O	20	243	High	High			3
11	46	O	9	157	Low	High	High	Low	4.2
12	45	O	10	132	High	High	High		3.6
13	45	O	7	141	High	High			0
14	63	O	17	173	High	High			3.2
15	37	O	20	148	Low	High			4.14
16	49	O	15	188	High	High	High		0
17	45	O	13	180	High	High			1
18	49	O	6	169	High	High	High	Low	7.5
19	44	O	17	196	High	High	High	Low	7.5

C: Cellular leiomyoma, D: Degenerated leiomyoma, O: Originary leiomyoma.

International Federation of Gynecology and Obstetrics (FIGO) stages were not significantly associated with SUVmax (Fig. 4). Patients with low SUVmax (<7.5) tended to have better overall survival, although the difference was not significant (Fig. 5).

Discussion

To diagnose uterine malignancy, cytological and histopathological examination of endometrial samplings is usually performed. However, some uterine sarcomas are difficult to diagnose preoperatively because they are arise from uterine muscle or mesenchymal tissue and are therefore not amenable to intrauterine sampling. Therefore, the issue of preoperative differentiation between leiomyoma and uterine sarcoma is important, as a correct diagnosis guides treatment decisions and determines whether any surgery should be by laparotomy or laparoscopy.

MRI is an appropriate tool for the diagnosis of leiomyoma, providing information on the number, location, and size of lesions. In the typical patient with leiomyomata, the lesions have the same T1-WI intensity on MRI as the myometrium, and lower intensity on T2-WI. However, degenerated leiomyomata show various findings depending on the type of degeneration. Hyaline degeneration has low-intensity on T2-WI, while mucoid degeneration shows sarcoma-like findings with high intensity on T1-WI. Uterine sarcomas show hemorrhage or necrosis with heterogeneous, high signal intensity on T2-WI and/or high intensity on T1-WI. In our study, all patients with leiomyomata had high intensity on T2-WI, and 9 patients had high intensity on DWI, which made it very difficult to differentiate uterine sarcoma from leiomyoma.

The use of DWI and the apparent diffusion coefficient (ADC) map is reportedly a good tool for differentiating between uterine sarcoma and leiomyoma [5,6]. Uterine sarcomas reportedly show high signal intensity on DWI and low ADC mapping. However, some leiomyomata exhibit confusing findings, with high intensity on DWI and low-signal ADC mapping, which leads to false-positive results. In our study, 4 patients in the leiomyoma group had high intensity on DWI and a low signal on ADC mapping. Sato et al. reported that DWI-negative findings can exclude benign leiomyoma, and the combination of DWI and ADC mapping is an effective diagnostic tool for differentiating between leiomyosarcoma and leiomyoma, with a sensitivity of 100%, specificity of 94.0%, PPV of 66.7%, NPV of 100%, and accuracy of 94.6% [6]. However, Namimoto et al. reported that ADC values overlap for benign leiomyoma and uterine sarcoma, although the mean ADC values of sarcomas are significantly lower than those of leiomyomata. Tamai et al. also reported that ADC values of uterine sarcomas overlap with those of

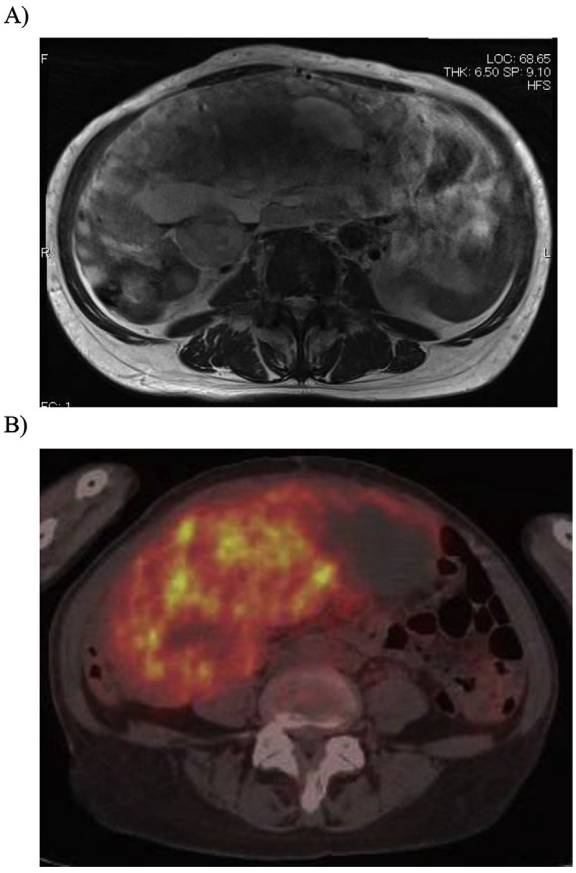

Fig. 1. A 57-year-old woman with leiomyosarcoma. (A) On the axial T2-weighted MRI, a heterogeneous, high intensity lesion plus low-intensity lesions were noted. B) An axial PET/CT image showed intense FDG uptake (SUVmax, 16).

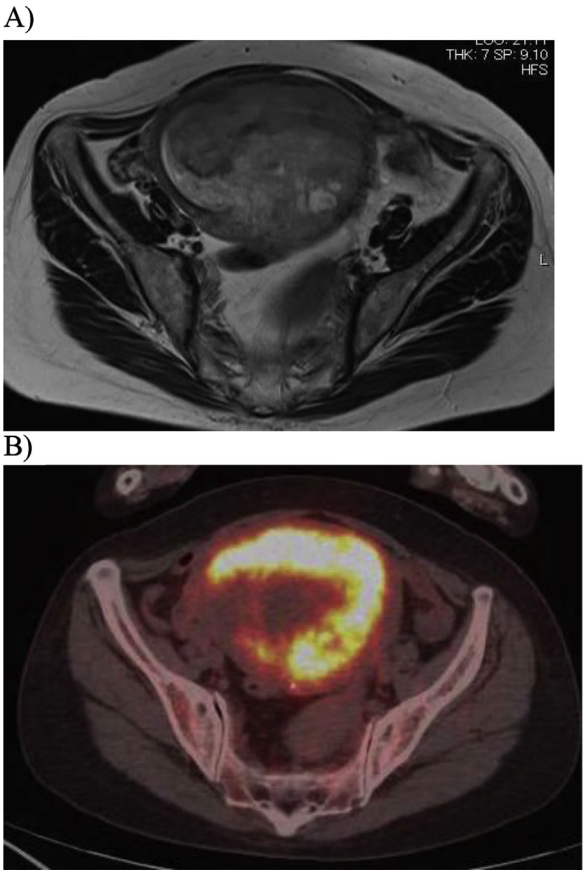

Fig. 2. A 70-year-old woman with undifferentiated endometrial sarcoma. A) On the axial T2-weighted MRI, a high intensity lesion plus low-intensity lesions were noted. B) An axial PET/CT image showed intense FDG uptake (SUVmax, 19.2).

cellular leiomyoma and ordinary leiomyoma, which indicates that ADC measurement has a limited role in distinguishing sarcoma from leiomyoma [5]. Furthermore, 1 of 7 sarcoma patients in their study had low signal intensity on DWI, indicating that negative DWI cannot exclude benign leiomyomata. Based on these findings, it is apparent that further diagnostic imaging is needed to differentiate between uterine sarcoma and leiomyoma.

PET/CT is a good diagnostic tool for uterine tumors; the optimal cutoff SUVmax is 7.5, with 73.3% sensitivity, 100% specificity, 100% PPV, and 82.6% NPV (area under the curve, 93.3%). The accuracy is improved by using the combination of PET/CT and LDH, with 86.6% sensitivity, 100% specificity, 100% PPV, and 90.4% NPV. With this combination, the number of unnecessary laparotomies can be decreased, and appropriate treatment can be determined in the preoperative period. The use of ^{18}F-FDG during PET detects malignant tumors, and the relative tissue-to-organ FDG uptake can be evaluated using the SUV. The first report of PET's efficacy in uterine sarcoma diagnosis was in a patient with metastatic leiomyosarcoma [7]. Since then, the efficacy of PET/CT to detect uterine sarcoma recurrence has been reported [3]; however, there are few reports on using the tool for the preoperative detection of uterine sarcoma [5,8–10]. Ramin et al. conducted a systematic review and meta-analysis on the use of PET for sarcoma diagnosis, concluding that PET is an accurate diagnostic tool with 92.1% sensitivity and 96.2% specificity for detection and localization of recurrence, but the efficacy of preoperative staging remains unknown due to limited studies [11].

Leiomyomata sometimes show focal FDG uptake on PET/CT in premenopausal women or in those with degenerative fibroids [12].

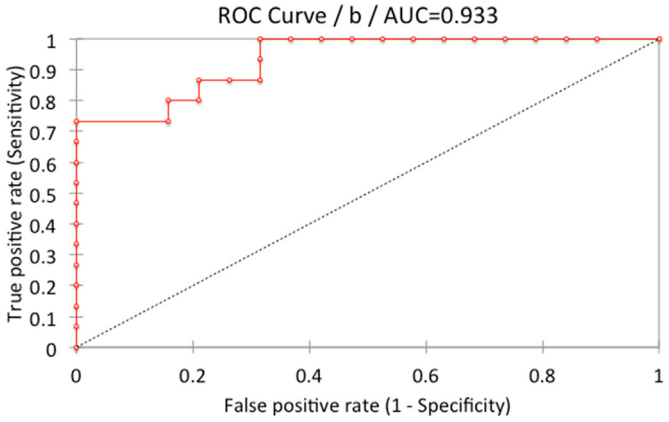

Fig. 3. Receiver operating characteristic curve. A maximum standardized uptake value (SUVmax) of greater than 7.5 was able to exclude leiomyoma with 73.3% sensitivity, 100% specificity, 100% positive predictive value, and 82.6% negative predictive value (area under the curve, 93.3%).

Nishizawa et al. reported that FDG uptake is observed in 10.4% of premenopausal women and in 1.2% of postmenopausal women, a significant difference [12]. FDG uptake is affected by the menstrual cycle and estrogen levels [13]; some leiomyomata with degeneration also show FDG uptake [14]. Therefore, PET alone may lead to a false diagnosis of malignancy.

For the purposes of differentiating sarcoma from leiomyoma, Goto et al. reported the efficacy of gadolinium-diethylenetriamine

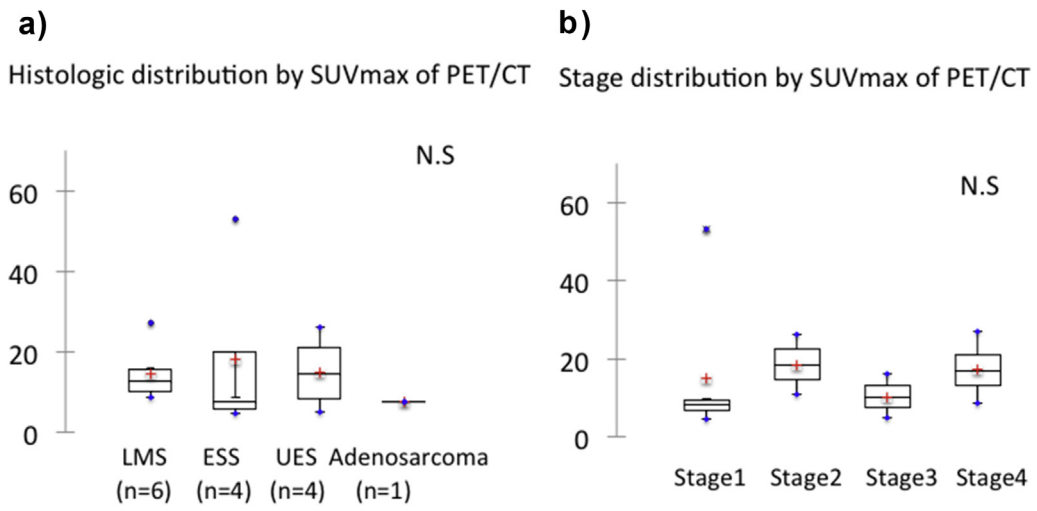

Fig. 4. Distribution of maximum standardized uptake value (SUVmax) on positron emission tomography/computed tomography (PET/CT). Distribution of histopathology and International Federation of Obstetrics and Gynecology (FIGO) stage using the optimal cutoff SUVmax was not significant. a) Histologic distribution by SUVmax. b) FIGO stage distribution.

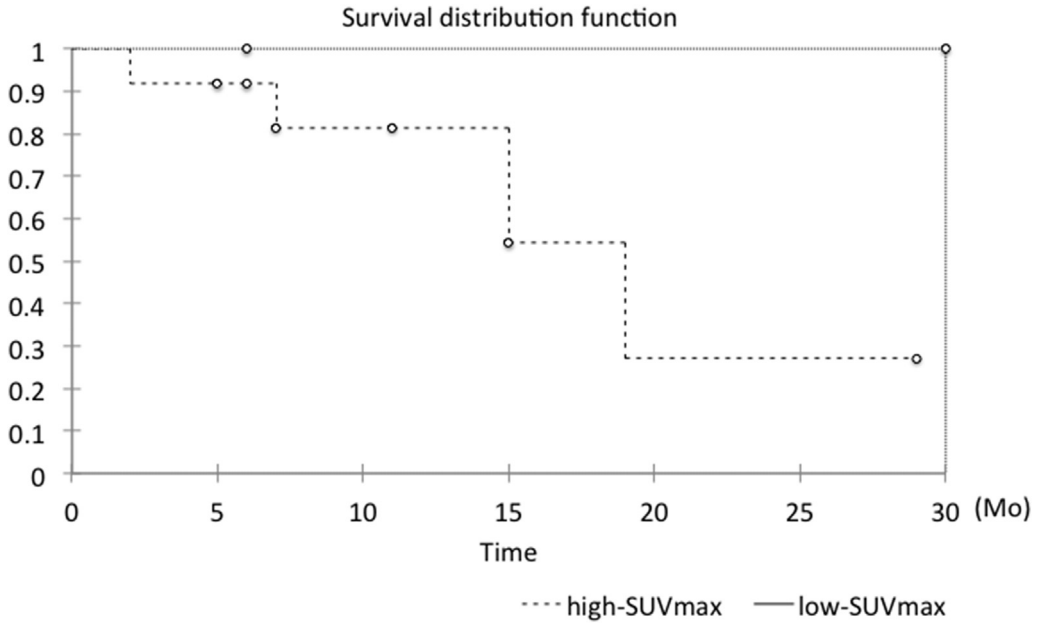

Fig. 5. Overall survival. Patients with a maximum standardized uptake value (SUVmax) < 7.5 tended to have better a prognosis, although the difference was not significant.

pentaacetic acid (Gd-DTPA) contrast-enhanced dynamic MRI combined with serum LDH and its isozymes [15]. In Goto's study, LDH was elevated in all patients with uterine sarcoma, with a sensitivity of 100% and a specificity of 87.7%, making it a good marker. In our study, the sensitivity and specificity of LDH was 53.3% and 86.3%, respectively, worse results than those previously reported. Nagamatsu et al. also reported the efficacy of the combination of PET/CT and LDH, with 100% sensitivity, 100% specificity, 100% accuracy, 100% PPV, and 100% NPV [16]. Based on their study and ours, the combination of PET/CT and LDH might be a promising diagnostic tool for differentiating uterine sarcoma from leiomyoma.

To our knowledge, our study is the first to show the efficacy of PET/CT by setting an optimal SUVmax cutoff for preoperative surveillance. PET/CT alone cannot detect uterine tumors; MRI is the gold standard tool for this purpose. Therefore, the addition of PET-CT is desirable when uterine sarcoma cannot be excluded on MRI.

We found no relation between histopathology or FIGO stage and the degree of FDG uptake on PET/CT. However, surgical outcome tended to be correlated with SUVmax, with a cutoff value of 7.5. There are no reports discussing the prognosis of patients with uterine sarcoma related to SUVmax. We need to accumulate more data in order to determine the exact nature of this relationship.

Our study is limited by its retrospective nature and small number of patients, given the rarity of the disease. Further investigation will be needed to clarify a more accurate cutoff SUVmax. We should also emphasize that our study excluded patients with carcinosarcoma, while most previous studies on uterine sarcoma included these patients [9,10,16,17]. Carcinosarcoma is now categorized and treated as a high-grade epithelial tumor [18].

In conclusion, when MRI is suspicious for uterine sarcoma, additional PET/CT with serum LDH can decrease the false-positive rate, using a cutoff SUVmax value of 7.5. This approach can help

to avoid unnecessary surgery in patients who may only have leiomyomata.

Conflict of interest

The authors declare that there are no conflicts of interest.

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